DIET AND NUTRITION*

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THE notion that diet and nutrition might influence cancer has been around for several decades, but got little attention during the past 20 to 30 years. During the 1930s a number of laboratories were genuinely interested in how nutrition might influence susceptibility to cancer, but the question lost both scientific and lay public attention. The National Cancer Institute recently initiated a program on diet, nutrition, and cancer, and, although funding is meager, implications are that the federal government and the general population are interested.

We should remember that food is the most complex mixture of chemicals to which we are exposed, but we actually know very little about the various mixtures we call our diet. We know that people and animals require various nutrients, but we know very little about how they interact, and we know even less about how contaminants contained in foods may, themselves, affect biological systems through interactions with essential nutrients or as single entities.

Despite our lack of knowledge, but with some important observations in hand, we can no longer doubt that an individual's nutritional status has an enormous influence on his capacity to respond to environmental stress, including carcinogens. The wide variation in incidence of some types of cancer in various ethnic groups living in different geographic locations (Table I) and the change in risk among migrant populations as they relocate and assume the dietary habits and nutritional status of low or high-risk groups strongly support this concept.[1-3] Table II indicates that of all new cases of cancer and of cancer deaths estimated for the United States in 1975, about a third are types which have been associated with nutrition in one way or another. This information has come primarily from epidemiological studies. Other factors which may be related to differences

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TABLE I. AGE-ADJUSTED DEATH RATE/100,000—1968-1969*

Country	Primary cancer site: Stomach Male	Stomach Female	Colon and rectum Male	Colon and rectum Female	Breast Female
United States	9	4	19	16	22
Japan	66	34	9	7	4
Scotland	23	12	25	21	26
Germany Fed. Rep.	33	18	21	17	19
Netherlands	26	13	18	17	26
Chile	59	36	7	7	11

*Compiled from data in References 1 to 3

TABLE II. CANCER, MORBIDITY AND MORTALITY IN UNITED STATES ASSOCIATED WITH DIET

Organ site	Estimated statistics for 1975: New cases	Deaths
Esophagus	7,400	6,500
Stomach	22,900	14,400
Colon	69,000	38,600
Breast	88,700	32,900
Liver (and bile ducts)	11,500	9,800
Total	199,500	102,200
All cancer	665,000	365,000

in cancer incidence are carcinogens or their precursors found as contaminants in foods. Mycotoxins, nitrosamines, pesticides, synthetic hormones, and a number of other chemicals such as food additives used to improve texture, flavor, color, or nutritional value are considered important, real, or potential factors. The association of nutritional deficiencies or imbalances and food contaminants or additives and a high incidence of some forms of cancer and the supporting experimental data strongly indicate a relation between nutrition and cancer. This has caught the attention of the scientific community in recent years and emphasized the important opportunity that nutrition provides in our continuing search for the cause and prevention of cancer.

Before we consider sites where cancer associated with diet occurs in the human body, we should examine changes in food habits and patterns of consumption which have taken place during the past several decades in the

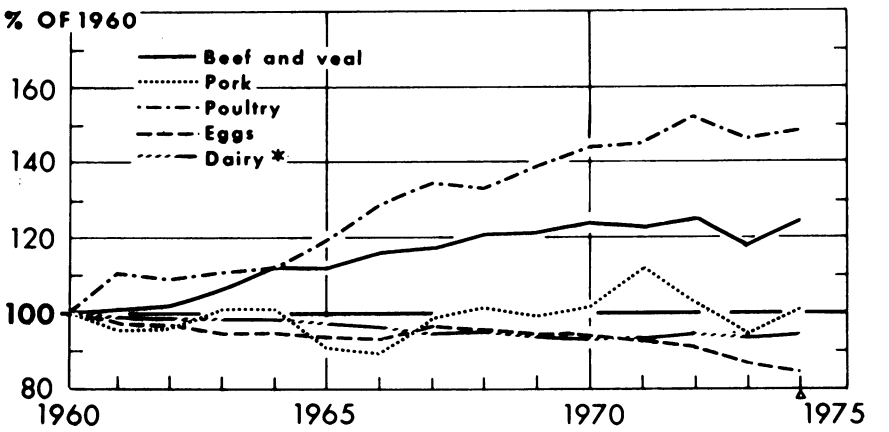

Fig. 1. Changes in per capita consumption (disappearance) of selected livestock products, 1960 to 1974.* Includes butter; preliminary. Reproduced by permission from Gortner, W. A.: Nutrition in the United States, 1900 to 1974. *Cancer Res. 35:*3251, 1975.

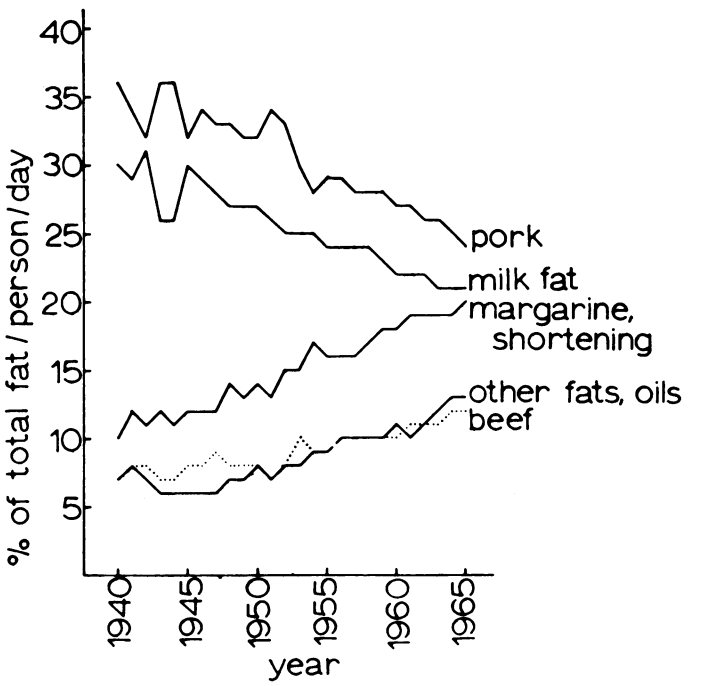

Fig. 2. Diet sources of fat, 1940 to 1965. Reproduced by permission from Gortner, W. A.: Nutrition in the United States, 1900 to 1974. *Cancer Res. 35:*3251, 1975.

TABLE III. CRUDE FIBER AND FOOD LIPIDS AVAILABLE PER CAPITA PER DAY IN THE UNITED STATES FOOD SUPPLY

Years	Total nutrient fat (g.)	Fatty acids			Cholesterol (mg.)	Crude fiber (g.)
		Saturated (g.)	Oleic acid (g.)	Linoleic acid (g.)		
1909-1913	125	50.3	51.5	10.7	509	6.1
1925-1929	135	53.3	55.2	12.5	524	5.8
1935-1939	133	52.9	54.5	12.7	493	5.5
1947-1949	141	54.4	58.0	14.8	577	4.9
1957-1959	143	54.7	58.2	16.6	578	4.4
1965	145	53.9	58.8	19.1	540	4.2
1970	157	55.9	63.1	23.3	556	4.2
1974	158	56.0	62.9	24.2		4.3

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United States. Figure 1 shows that animal products, except for eggs, have been consumed in increasing quantity since 1960. Very likely, the decline in egg consumption is, at least in part, a result of the successful American Heart Association campaign against eating cholesterol and fats as a deterrent to cardiovascular disease. It is probably quite important that the consumption of animal products, in part beef, has sharply increased, providing more saturated fat and cholesterol. Figure 2 shows the trends in the types of fats consumed; pork and dairy fat have decreased and beef and vegetable fat increased. Table III illustrates the quantities of crude fiber and food lipids available per capita in the United States and how that has changed over the last 50 to 60 years. Around 1910 about 125 g. a day of total fat were available; it has increased to about 160 in 1974. That is a remarkable increase in the amount of fat eaten. Accompanying that, of course, has been an increase in fatty acids, both saturated and unsaturated, and an increase in cholesterol. This has been accompanied by a decrease in consumption of crude fiber from about 6 g. down to about 4 g. a day, and that may well be important in terms of gastrointestinal tract motility and other aspects of disease of the gastrointestinal tract.

A sex difference generally exists in the incidence rate of cancer in man and animals, particularly notable in some animal species. Figure 3 shows that male and female daily fat consumption stays about the same until children are eight or nine years old and then separates. Female fat con-

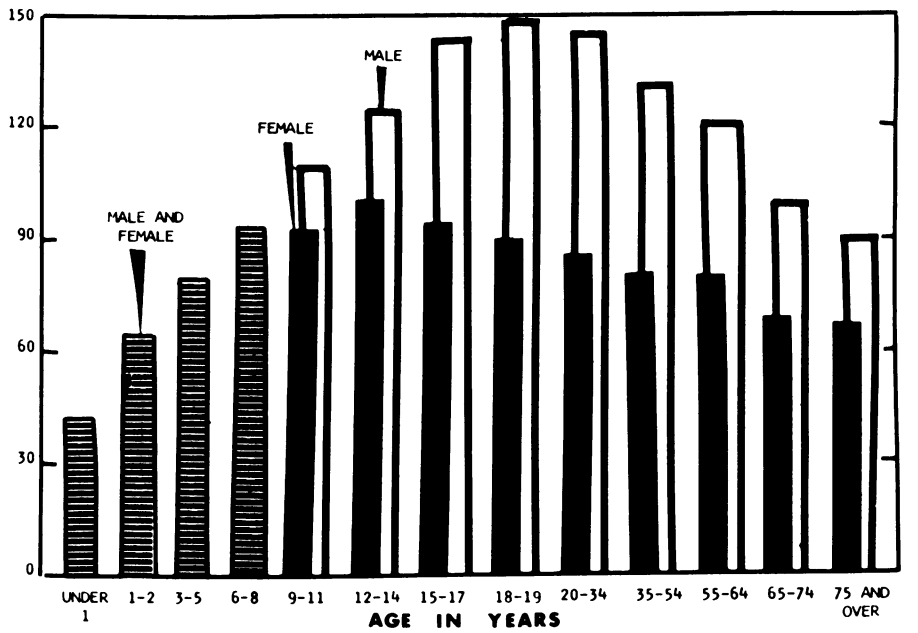

Fig. 3. Grams of fat from one day's diet in 1965, by age and sex. Reproduced by permission from Gortner, W. A.: Nutrition in the United States, 1900 to 1974. *Cancer Res. 35*:3249, 1975.

sumption plateaus and then starts to decline at 12 to 14 years of age, whereas the male continues to go up and finally declines after 20 years of age. This may be associated in some as yet unknown way with differences in susceptibility to cancer later in life. Food habits have changed gradually[4] during the past 40 years, a period during which cancer has increased in some populations.

In the United States[5] significant correlations between esophageal cancer, the percentage of the population living in urban communities, and cigarette and alcohol sales have been demonstrated. A geographic correlation between mortality rates from esophageal cancer and per capita consumption of spirits and beer has also been shown.[6] Alcoholics often have vitamin and zinc or iron deficiencies, all of which may contribute to tumor development.[7,8]

An association of low intake of vitamins A, C, and riboflavin, animal protein, and fresh fruit and vegetables and an increased incidence of

TABLE IV. TUMOR INCIDENCE IN RATS FED N-NITROSODIETHYLAMINE

Diet	No. of rats	N-Nitroso-diethylamine intake (total mg./rat)	Body wt. (g.)	% of rats with tumor in: Eso-phagus	Liver	Blad-der	Lung	Other organ
Control	23	179	657	35	70	0	4	26
Marginal lipotrope	34	176	702	44	88	3	9	47

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esophageal cancer has been established in Iran.[9]. These studies also demonstrate a relation between esophageal cancer and wheat-eating, as opposed to rice-eating populations. In China a high incidence of esophageal cancer in both chickens and people has been reported from well-defined areas of the Peoples Republic of China,[10,11] where wheat is eaten in preference to rice. In the geographic areas of very high incidence the predominance of esophageal cancer in men decreases with age and women have an equal or even slightly greater incidence as they grow older. In these areas of high incidence, as in Iran, association with tobacco and alcohol is less strong. Women may be more susceptible to other environmental carcinogens than men, and such other factors as deficiency concomitant to childbearing and poor intake of nutrients from poverty coexist in many of these populations.[11]

Animal studies in our laboratories have provided data which suggest that deficiencies and dietary contamination may interact in esophageal carcinogenesis. We have examined the effects of feeding N-nitrosodiethylamine (DEN) to lipotrope-deficient rats[12] and have found significant enhancement of esophageal carcinogenesis (Table IV). The tumors induced in these investigations were invasive squamous cell carcinomas, morphologically identical to those in man. However, it must be pointed out that in this study the rats' diet was also high in fat. Recent studies by our group, in esophageal cancer patients in Hong Kong and in animal studies,[13] clearly show that zinc and copper are important in resistance to esophageal cancer.

GASTRIC CANCER

Populations in Japan, Chile, Colombia, Austria, Iceland, and Finland have a high incidence of gastric cancer while a low incidence is recorded

TABLE V. RATES OF MORTALITY FROM CANCER OF GASTROINTESTINAL SITES AT AGES 0 TO 74 YEARS FOR JAPANESE IN JAPAN AND JAPANESE AND CAUCASIANS IN CALIFORNIA

	Japan		California					
	(Japanese)		*Foreign-born*		*U.S.-born*		*Caucasian*	
	Men	*Women*	*Men*	*Women*	*Men*	*Women*	*Men*	*Women*
Stomach (151)	58.4	30.9	29.9	13.0	11.7	11.3	8.0	4.0
Colon (153)	1.9	2.1	6.1	7.0	6.3	10.4	7.9	8.3
Rectum (154)	3.3	2.8	4.0	(4.0)	(3.1)	(2.0)	4.2	2.8
	63.6	35.8	40.0	24.0	21.1	23.7	20.1	15.1

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in the United States and Canada.[1] Many dietary factors are implicated in its etiology but studies of food habits among gastric cancer patients have identified few significant differences in intake of specific nutrients compared to control groups.[14-16] The high incidence of gastric cancer in Iceland has been associated with a large intake of smoked food but this has not been substantiated.[17] Talc, most of which contains asbestos, and which sometimes is used as a coating on rice, has been assigned a role in stomach cancer in Japan,[18] but this requires considerable supporting epidemiologic data and experimental work.

Mortality from gastric cancer in the United States has decreased dramatically during the past four decades. In gastric cancer, frequency gradually increases with decreasing socioeconomic status, and the lowest socioeconomic groups have three times the incidence of more privileged social groups.[19] Stomach cancer among Japanese migrants to Hawaii about equals their native Japanese cohorts in high-risk areas, even though immigrants eat western diets, but their offspring have lower risks.[20] In an American study it was found that gastric cancer patients ate raw vegetables less often than controls, but there was no relation between fried foods, meats, or alcohol consumption, and the disease.[21] Recent Japanese studies indicate a consumption of milk and milk products increased more than 20 times over the past two decades,[22] which may be related to the decline in gastric cancer.

Cancer of the stomach and cancer of the colon are inversely related. Migration from a high-risk area for stomach cancer in Japan to a relatively

low-risk area of California resulted in decreased gastric cancer and increased colon cancer,[23,24] but in both cases the incidence among the migrants tended to assume the incidence of the area to which they migrated (Table V).

Although evidence suggests that nutrition is related to gastric cancer in some human populations, specific agents still remain unknown and, in the case of animal experiments, evidence is variable and sometimes conflicting.

Colon Cancer

Gastric and colon cancer are negatively correlated, that is, where one is relatively common the other is usually rare. Cancer of the colon is associated with environmental factors and a number of studies suggest a role for nutrition in the etiology of this malignancy. The mortality from colon cancer, for example, is high in Scotland, Canada, and the United States and low in Japan and Chile.[1]

Epidemiological studies implicate a high-fat diet in the etiology of colon cancer, but these same populations usually eat considerable protein because most dietary fat is eaten along with animal protein (beef).[25] In Japan, where the incidence of colon cancer is low, fat intake accounts for about 12% of calories and the fat is primarily unsaturated. In the United States 40 to 44% of calories are derived from fat, including the diet eaten by immigrants to the United States from Japan.[26,27] In contrast to gastric cancer, colon-cancer incidence rises in the immigrants, and their children have a much higher incidence of colon cancer than those born in Japan. Changing to a western diet and a higher standard of living may account for this difference. The incidence of colon cancer in the United States does not vary appreciably with race, ethnic group, or socioeconomic status.[2,3] Mortality from colon cancer in migrants from Poland and Norway to the United States has shifted upward to American levels. Bjelke[28] reported a negative correlation in Norway between blood-cholesterol levels and mortality from colon cancer, with a particularly high risk of colon cancer in people eating an excess of processed meats. A high incidence of colon cancer appears among populations which have diets high in refined foods and low in fiber. Refined foods result in small stools and long intestinal transit time, while high-fiber diets are associated with large stools, rapid transit time, and differences in bacterial flora.[29-34] Anaerobic bacteria counts are higher and aerobic bacteria lower; levels of total neutral steroids

TABLE VI. INCIDENCE OF LIVER AND COLON TUMORS IN RATS FED AFLATOXIN B_1 AND VARIOUS LEVELS OF VITAMIN A

	Animal No.	*Sex*	*Liver*	*Colon*
Control				
3.0 μg/g. RA_1	1-24	M	0/24	0/24
3.0 μg/g. RA	25-51	F	0/26	0/26
3.0 μg/g. RA + AFB_1	52-76	M	21/24	1/24
3.0 μg/g. RA + AFB_1	77-101	F	19/24	2/24
Low vitamin A				
0.3 μg/g. RA	102-111	M	0/10	0/10
0.3 μg/g. RA	112-123	F	0/12	0/12
0.3 μg/g. RA + AFB_1	124-190	M	59/66	19/66
0.3 μg/g. RA + AFB_1	191-232	F	32/42	12/42
High vitamin A				
30.0 μg/g. RA	233-255	M	0/23	0/23
30.0 μg/g. RA	256-275	F	0/20	0/20
30.0 μg/g. RA + AFB_1	276-301	M	24/26	2/26
30.0 μg/g. RA + AFB_1	302-332	F	26/31	3/31

RA = retinyl acetate (vitamin A)
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and degraded cholesterol and bile acids are higher in feces of individuals from areas of high risk for colon cancer.[35] Some metabolites of bile salts may be carcinogenic. Thus, as these more recent observations illustrate, the relation of a number of dietary habits and constituents to colon cancer is complex.

Cancer of the colon occurs rarely as a spontaneous disease in laboratory animals but can be readily induced by a number of chemical carcinogens. Aflatoxin,[36] a potent liver-cell carcinogen, can cause colon cancer in laboratory animals when the diet is low in Vitamin A (Table VI), which suggests a change in sensitivity of the colon or a change in metabolites associated with vitamin A deficiency. This may be mediated through a change in gut microflora, a change in drug-metabolizing enzymes, altered quantity or quality of the secretion of vitamin A-dependent colon glycopeptides,[37] or a combination of these, all of which are diet-sensitive and are involved in some aspects of cancer induction.

Recent studies[38,39] have clearly shown that intestinal aryl hydrocarbon hydroxylase can be modified by diet, which in turn can modify chemical carcinogenesis. The activity of aryl hydrocarbon hydroxylase in the rat intestine can be changed by exogenous inducers in foods, including Brus-

sels sprouts, turnips, cabbage, alfalfa, and other dietary components, suggesting an important role for nutrients in resistance to cancer.

Breast Cancer

Breast-cancer incidence has been correlated with socioeconomic status, overnourishment, and weight and body mass.[40,41] It is not common among women in developing societies nor in Japanese women but the incidence increases in these population groups when they migrate to the United States.[42] Breast cancer is increasing among young women in the United States. This has been attributed to increased fat consumption, but evidence at this time is insufficient to incriminate fat *per se* in breast cancer. Further, increased fat intake in the United States is almost always accompanied by increased protein intake.

An interesting possible mechanism for increased breast cancer associated with fat is related to the intestinal bacterial flora. People consuming a western high-fat diet have a higher proportion of strictly anaerobic microflora in the intestine, organisms which can produce estrogens from biliary steroids. These are increased in subjects consuming high-fat diets.[33]

Other dietary factors have been associated with breast cancer in epidemiologic studies, including iodine deficiency,[43] the cadmium content of the water,[44] and high rate of beer consumption. These suggestions are speculative, however, and require more extensive epidemiologic and experimental support.

Discussion

Recognition that there are factors in the diet which can profoundly influence individual susceptibility to cancer is a first step toward utilizing these mechanisms to protect populations from unidentified carcinogens or from those that are known and for various reasons cannot be eliminated as a health hazard. Epidemiologic studies and animal experimentation clearly indicate a critical need to learn more about how dietary factors affect people so that they can be used in the prevention of cancer.

Changing people's eating habits offers one of the most exciting means to change the course of cancer morbidity and mortality. There can be no doubt that in many population groups dietary habits are central to the incidence of some forms of cancer, and through astute observation and experimentation we can learn to use nutrition as a major modifier in our efforts toward cancer prevention.

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